REMARKS

Introductory Comments:

Claims 1-30 were examined in the Office Action dated October 31, 2001 and rejected under (1) 35 U.S.C. §112, second paragraph as indefinite (claims 4, 11-13 and 17); (2) 35 U.S.C. §112, first paragraph, as nonenabled (claims 14-27); (3) 35 U.S.C. §101 for double patenting (claims 28-30); and (4) the judicially created doctrine of obviousness-type double patenting (claims 1-13). These rejections are believed to be overcome by the above amendments and are otherwise traversed for reasons discussed below.

Overview of the Above Amendments:

The specification has been amended, as requested by the Office, to capitalize trademarks.

Claims 5, 8, 11-13, 17 and 27-30 have been canceled in order to advance prosecution. Cancellation is without prejudice, without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record. Applicants expressly reserve the right to file one or more continuing applications hereof containing the canceled claims.

Claims 1, 4, 6, 7 and 14 have been amended in order to recite the invention with greater particularity. Specifically, claim 1 now recites that the antigen is from HIV. Claim 4 has been amended to replace the terms "Tween 80®" and "Span 85®" with the terms "polyoxyethylene sorbitan monooleate" and "sorbitan trioleate," respectively. Claims 6 and 7 have been amended to depend from claim 1 rather than from canceled claim 5. Claim 14 has been amended to recite a method of "inducing an immune response" as suggested by the Office.

Support for these amendments can be found in the claims as filed as well as throughout the specification at, e.g., page 16, lines 3-7; page 22, line 33 to page 23, line 4. See also pages 957 and 1807 of the *Sigma Catalog: Biochemicals and Reagents for Life Science Research* (1999) which detail the chemical names for Tween and Span.

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New claims 31 and 32 have been added and depend from claims 1 and 14, respectively. These claims recite that the composition further comprises MTP-PE (N-acetylmuramyl-L-alanyl-D-isogluatminyl-L-alanine-2-(l'-2'-dipalmitoyl-*sn*-glycero-3-huydroxyphosphoryloxy)-ethylamine). Support for these new claims may be found in claims 11 and 17 as filed, as well as throughout the specification at, e.g., page 23, lines 20-22.

No new matter has been added to the application by way of the foregoing amendments and new claims.

Rejections Under 35 U.S.C. §112, Second Paragraph:

Claims 4, 11-13 and 17 were rejected as indefinite under 35 U.S.C. §112, second paragraph. Specifically, the Office objected to the use of trademarked names for the chemical reagents. As discussed above, claim 4 has been amended per the Examiner's suggestions. Particularly, the terms "Tween 80®" and "Span 85®" have been replaced with the terms "polyoxyethylene sorbitan monooleate" and "sorbitan trioleate," respectively. None of the remaining claims include trademarked names. Accordingly, this basis for rejection has been overcome and withdrawal thereof is respectfully requested.

Rejections Under 35 U.S.C. §112, First Paragraph:

Claims 14-27 were rejected under 35 U.S.C. §112, first paragraph, as nonenabled. The Office acknowledges that the specification is enabling for "a method of inducing an immune response" (Office Action, page 3), but argues that claims directed to "a method of immunizing" are not enabled. Although applicants believe methods of immunizing to be fully enabled, independent claim 14 now reads that the method is one for "inducing an immune response." Thus, this basis for rejection is overcome and withdrawal thereof is respectfully requested.

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The Double Patenting Rejections:

Claims 28-30 were rejected under 35 U.S.C. §101 as claiming the same invention as that of claims 12-14 of U.S. Patent No. 6,086,901. Applicants have canceled claims 28-30.

Claims 1-13 and 14-27 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 6,086,901 and claims 1-11 of U.S. Patent No. 6,306,405, respectively. Applicants are submitting a Terminal Disclaimer, as requested by the Office.

Accordingly, the above bases for rejection are overcome and withdrawal thereof is respectfully requested.

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CONCLUSION

Applicants respectfully submit that the claims are novel and nonobvious and comply with the requirements of 35 U.S.C. §112. Thus, allowance is believed to be in order and an early notification to that effect would be appreciated.

Please direct all further written communications regarding this application to:

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Paragraph beginning on page 3, line 9 has been amended as follows:

One lipophilic derivative of MDP is N-acetylmuramyl-L-alanyl-D-isogluatminyl-L-alanine-2-(l'-2'-dipalmitoyl-*sn*-glycero-3-huydroxyphosphoryloxy)-ethylamine (MTP-PE). This muramyl tripeptide includes phospholipid tails that allow association of the hydrophobic portion of the molecule with a lipid environment while the muramyl peptide portion associates with the aqueous environment. Thus, the MTP-PE itself is able to act as an emulsifying agent to generate stable oil-in-water emulsions. MTP-PE has been used in an emulsion of 4% squalene with 0.008% TWEEN 80® [Tween® 80], termed MTP-PE-LO (low oil), to deliver the herpes simplex virus gD antigen with effective results (Sanchez-Pescador et al., *J. Immunol.* (1988) 141:1720-1727), albeit poor physical stability. Recently, MF59, a safe, highly immunogenic, submicron oil-in-water emulsion which contains 4-5% w/v squalene, 0.5% w/v TWEEN 80® [Tween® 80], 0.5% SPAN 85® [Span® 85], and optionally, varying amounts of MTP-PE, has been developed for use in vaccine compositions. See, e.g., Ott et al., "MF59 -- Design and Evaluation of a Safe and Potent Adjuvant for Human Vaccines" in *Vaccine Design: The Subunit and Adjuvant Approach* (Powell, M.F. and Newman, M.J. eds.) Plenum Press, New York, 1995, pp. 277-296.

Paragraph beginning on page 6, line 5 has been amended as follows:

In another embodiment, the invention is directed to a composition comprising (a) a submicron oil-in-water emulsion which comprises 4-5% w/v squalene, 0.25-0.5% w/v TWEEN 80® [Tween 80®], and 0.5% w/v SPAN 85® [Span 85®], and optionally, N-acetylmuramyl-L-alanyl-D-isogluatminyl-L-alanine-2-(l'-2'-dipalmitoyl-*sn*-glycero-3-huydroxyphosphoryloxy)-ethylamine, and (b) a selected antigen entrapped in, or adsorbed to, a biodegradable microparticle.

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Paragraph beginning on page 22, line 33 has been amended as follows:

Emulsifying agents suitable for use in the oil-in-water formulations include, without limitation, sorbitan-based non-ionic surfactants such as those commercially available under the name of SPAN® [Span®] or ARLACEL® [Arlacel®]; polyoxyethylene sorbitan monoesters and polyoxyethylene sorbitan triesters, commercially known by the name TWEEN® [Tween®]; polyoxyethylene fatty acids available under the name MYRJ® [Myrj®]; polyoxyethylene fatty acid ethers derived from lauryl, acetyl, stearyl and oleyl alcohols, such as those known by the name of BRIJ® [Brij®]; and the like. These substances are readily available from a number of commercial sources, including ICI America's Inc., Wilmington, DE. These emulsifying agents may be used alone or in combination. The emulsifying agent will usually be present in an amount of 0.02% to about 2.5% by weight (w/w), preferably 0.05% to about 1%, and most preferably 0.01% to about 0.5. The amount present will generally be about 20-30% of the weight of the oil used.

Paragraph beginning on page 25, line 9 has been amended as follows:

Particularly preferred submicron oil-in-water emulsions for use herein are squalene/water emulsions optionally containing varying amounts of MTP-PE, such as the submicron oil-in-water emulsion known as "MF59" (International Publication No. WO 90/14837; Ott et al., "MF59 -- Design and Evaluation of a Safe and Potent Adjuvant for Human Vaccines" in *Vaccine Design: The Subunit and Adjuvant Approach* (Powell, M.F. and Newman, M.J. eds.) Plenum Press, New York, 1995, pp. 277-296). MF59 contains 4-5% w/v Squalene (e.g., 4.3%), 0.25-0.5% w/v TWEEN 80® [Tween 80®], and 0.5% w/v SPAN 85® [Span 85®] and optionally contains various amounts of MTP-PE, formulated into submicron particles using a microfluidizer such as Model 110Y microfluidizer (Microfluidics, Newton, MA). For example, MTP-PE may be present in an amount of about 0-500 μg/dose, more preferably 0-250 μg/dose and most preferably, 0-100 μg/dose. MF59-0, therefore, refers to the above submicron oil-in-water emulsion lacking MTP-PE, while MF59-100 contains 100 μg MTP-PE per dose. MF69, another submicron oil-in-water emulsion for use herein, contains 4.3% w/v squalene, 0.25% w/v

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TWEEN 80® [Tween 80®], and 0.75% w/v SPAN 85® [Span 85®] an optionally MTP-PE. Yet another submicron oil-in-water emulsion is SAF, containing 10% squalene, 0.4% TWEEN 80® [Tween 80®], 5% pluronic-blocked polymer L121, and thr-MDP, also microfluidized into a submicron emulsion.

In the Claims:

Claims 1, 4, 6, 7 and 14 have been amended as follows:

1. (Amended) A composition comprising a submicron oil-in-water emulsion, and a selected antigen entrapped in, or adsorbed to, a biodegradable microparticle, wherein the antigen is an HIV antigen.

4. (Amended) The composition of claim 1, wherein the submicron oil-in-water emulsion comprises 4-5% w/v squalene, 0.25-0.5% w/v polyoxyethylene sorbitan monooleate [Tween 80®], and 0.5% w/v sorbitan trioleate [Span 85®], and optionally, N-acetylmuramyl-L-alanyl-D-isogluatminyl-L-alanine-2-(l'-2'-dipalmitoyl-*sn*-glycero-3-huydroxyphosphoryloxy)-ethylamine.

6. (Amended) The composition of claim [5] 1, wherein the selected antigen is gp120.

7. (Amended) The composition of claim [5] 1, wherein the selected antigen is p24gag.

14. (Amended) A method of [immunization] inducing an immune response which comprises administering to a vertebrate subject (a) a submicron oil-in-water emulsion, and (b) a therapeutically effective amount of a selected antigen entrapped in, or adsorbed to, a biodegradable microparticle.

Claims 5, 8, 11-13, 17 and 27-30 have been canceled.

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New claims 31 and 32 have been added:

--31. (New) The composition of claim 1, wherein the submicron oil-in-water emulsion further comprises N-acetylmuramyl-L-alanyl-D-isogluatminyl-L-alanine-2-(l'-2'-dipalmitoyl-*sn*-glycero-3-huydroxyphosphoryloxy)-ethylamine.

32. (New) The method of claim 14, wherein the submicron oil-in-water emulsion further comprises N-acetylmuramyl-L-alanyl-D-isogluatminyl-L-alanine-2-(l'-2'-dipalmitoyl-*sn*-glycero-3-huydroxyphosphoryloxy)-ethylamine.--